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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,843	HAGEN, FREDERICK S.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *11,14-35 and 47-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,13 and 36-46* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☒ Claim(s) *1-54* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/07; 9/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-54 are pending in the instant application.

Elections of Species

In the 7/6/07 Office Action, five separate elections of species were required.

Applicant's elections of the species of (1) angiotensin converting enzyme (ACE); (2) diabetes; (3) small molecule; (4) no election possible; (5) serum in the reply filed on 1/7/08 is acknowledged.

Applicants state "[c]laims 1-10, 12, 13 and 36-46 are believed to readable on the elected species of invention". The Examiner agrees with this statement.

Claims 11, 14-35 and 47-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

With respect to the fourth species election, Applicants state "no election was made in regard to the presentation molecule as peptide was not elected as the agent. The presentation molecule is only used in association with screening for a peptide agent that alters processing of a membrane protein of interest". The Examiner has fully considered these statements. In view of Applicants' election of "small molecule" for the third species election, the Examiner withdraws the previous requirement for the fourth species election. However, it is noted that this requirement will be reinstated if any claims encompassing the species of "protein" are subsequently rejoined.

Claims 1-10, 12, 13 and 36-46 are under consideration, in so far as they are drawn to the elected species.

Claim Objections

Claim 1 is objected to because of the following informalities:

Claim 1 does not end with a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12, 13, 36, 37 and 39-46 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for identifying an agent that alters processing of a membrane protein of interest, comprising contacting the agent with an isolated animal host cell that expresses the membrane protein and at least one processing enzyme of the membrane protein, or a non-isolated host cell in a transgenic mouse expressing hAPP and an processing enzyme thereof, or a non-isolated host cell that naturally expresses the membrane protein and at least one processing enzyme of the membrane protein, and detecting altered processing of the membrane protein to identify the agent that alters the processing of the membrane protein,

does not reasonably provide enablement for a method for identifying an agent that alters processing of a membrane protein of interest, comprising contacting the agent with an animal host cell that expresses the membrane protein and at least one processing enzyme of the membrane protein, and detecting altered processing of the membrane protein to identify the agent that alters the processing of the membrane protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of screening comprising contacting an agent with cells expressing a membrane protein and at least one processing enzyme of the membrane protein, and detecting altered processing of the membrane protein. The methods encompass use of a genus of host cells, including those that naturally express, or recombinantly, express the membrane protein and/or enzyme. Furthermore, the genus of host cells includes both isolated host cells, as well as those that are found with an organism. Furthermore, the genus of host cells encompasses cells from any animal species, including humans.

The specification asserts that the claimed screening methods can be performed in transgenic animals. The specification provides examples of transgenic mice expressing human amyloid precursor protein (hAPP) that were known in the art, and can be used in the claimed method of screening. However, there are no methods or working examples disclosed in the instant application whereby any multicellular animal other than mice expressing hAPP is demonstrated to express the encoded peptide. The unpredictability of the art is *very high* with regards to making transgenic animals. The literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome that may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals, including transgenic humans, according to the instant invention. Furthermore, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines

in a number of species…However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells that can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing a membrane protein and/or secretase, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 12, 13 and 36-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Hooper et al, 1997. Biochem J. 321: 265-279 (cited on the 9/26/07 IDS).

The recitation of “for identifying an agent that alters processing of a membrane protein of interest” in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. As such, claim 1 encompass any method comprising contacting an "agent" with an animal host cell that expresses both a membrane protein and a processing enzyme of the membrane protein, and detecting altered processing of the membrane protein.

Hooper teaches in a section titled "Secretase Assays" that "[t]he majority of studies on membrane protein secretases have employed whole-cell systems utilizing either natural or recombinant cell lines that express both the membrane protein and its secretase" (pg 275). Hooper further teaches, "…release of TGF-α, L-selectin, IL6R and APP from the surface of CHO cells can be blocked by both metallo-protease inhibitors (TAPI-2 and 1,10-phenanthroline) and serine-protease inhibitors..." CHO cells are animal cells. Thus, Hooper teaches a method that comprises contacting an agent (e.g., a metallo- or serine protease inhibitor) with CHO animal cells that express a membrane protein (e.g., APP) and its secretase and detecting altered (e.g., blocked) processing when the cell is contacted with an agent (metallo-protease or serine-protease inhibitors). Hooper further teaches that the elected species of membrane protein under consideration, ACE, cleavage is inhibited by TAPI-2, BB94 (batimastat) and BB2116. These teachings of Hooper anticipate claim 1.

Claims 2 and 3 each encompasses a method of claim 1 wherein the detecting of the altered processing comprises assessing the relative presence of a membrane protein fragment released from the surface of the cell. In the teachings of Hooper described above, the blockage of release of the ectodomain of the membrane proteins indicates that the relative presence of the membrane protein fragment has been detected; therefore, the teachings of Hooper described above also anticipate claims 2 and 3.

Claim 4 depends from claim 1 and encompasses "a membrane protein processing enzyme" that is "a protease". The teachings of Hooper described are

inherently directed to an enzyme that is a protease because the release is blocked by protease inhibitors; therefore, the teachings of Hooper also anticipate claim 4.

Claim 5 depends from claim 1 and recites "wherein the altered membrane protein processing results in a decreased production of a fragment of the membrane protein released from the cell surface". In the teachings of Hooper described above, the blockage of release of the ectodomain of the membrane proteins inherently results in decreased production of the released fragment; therefore, the teachings of Hooper described above also anticipate claim 5.

Claims 6 and 7 depend from claim 5 and limit the released fragment to one that is "associated with an increased risk of disease" (claim 6) and further wherein the disease is Alzheimer's (claim 7). Hooper teaches that the released APP fragment (known as βA4) is associated with an increased risk of Alzheimer's disease (pg 268, "[t]he deposition of βA4 is currently believed to be the central pathological event in the development of Alzheimer's disease)". Therefore, the teachings of Hooper described above also anticipate claims 6 and 7.

Claim 12 depends from claim 1 and limits the agent to a "small molecule". The inhibitors described by Hooper, TAPI-2 and 1,10-phenanthroline, are each small molecules. As such, the teachings of Hooper described above also anticipate claim 12.

Claim 13 depends from claim 1 and limits the agent to a "biomolecules". The specification teaches that biomolecules includes molecules that exist or can be produced by living systems "as well as structures derived from such molecules" ([¶ 46 of the published application]). Hooper further teaches that "the effect of various agents (e.g., phorbol esters, transport inhibitors, etc) on the activity of the secretase can be studied" (pg 275). Phorbol compounds are plant-derived, and phorbol esters are derived from such; therefore, the teachings of Hooper also anticipate claim 13.

Claims 36-38 each depends from claim 1 and limit the host cell to either a mammalian (claim 36), a recombinant (claim 37) or an isolated host cell (claim 38). As described above, Hooper teaches use of assays using "recombinant cell lines" (which are recombinant and isolated) and "CHO cells" which are mammalian. Therefore, the teachings of Hooper described above also anticipate claims 36-38.

Claim 39 depends from claim 1 and limits the method to one "wherein the agent is contacted with the host cell under substantially physiological conditions". The specification teaches (¶ 65) that such conditions refer to those that "are normally present, or that substantially approximate those normally present, in an extracellular space, on an extracellular surface (e.g., on a cell membrane), in a Golgi network, secretory vesicle, and/or in a complex biological fluid". As such, the phrase "substantially physiological condition" broadly encompasses any screening that takes place with a cell-bound membrane protein, because such is "on an extracellular surface". As such, the teachings of Hooper described above also anticipate claim 39.

Claims 40 and 41 depend from claim 39 and each encompass conditions comprising the presence of "serum". The screening methods taught by Hooper with CHO cells inherently comprise serum in the form of fetal bovine serum. In describing the CHO cell assays, Hooper references (on pg 276) Arribas et al (1996; Journal of Biological Chemistry. 271(9): 11376-11382; cited here solely to support inherency). Arribas teaches that the cell medium used in the assays was "supplemented with 10% fetal bovine serum" (pg 11377). Therefore, the teachings of Hooper with respect to CHO cell assays inherently comprise serum, and therefore the teachings of Hooper also anticipate claims 40 and 41.

Claims 42-44 depend from claim 2 and each encompass the embodiment recited in claim 44, wherein the membrane protein fragment presence is assessed using at least two labeled antibodies for two different epitopes of the membrane protein or a membrane protein fragment. The screening methods taught by Hooper with CHO cells inherently comprises measurements of ectodomain shedding using two labeled antibodies, including one that binds the extracellular domain (ectodomain) and one that binds the cytoplasmic domain. In describing the assays, Hooper references (on pg 276) Arribas et al (cited above). Arribas teaches, for example, in Figure 3 that "cells were immunostained with antibodies against the L-selectin ectodomain or the HA epitope and analyzed by flow cytometry" (pg 11379). Therefore, the teachings of Hooper also anticipate claims 42-44.

Claim 45 depends from claim 1 and limits the agent to "allosteric effector of the membrane protein". The specification does not provide a limiting definition of the term allosteric effector. Therefore, the term is interpreted broadly to encompass any agent that changes the structure of the membrane protein. As such, this term encompasses the protease inhibitors described above, because inhibition of the cleavage of the membrane protein produced by these inhibitors results in a different structure; i.e., an intact membrane protein.

Claim 46 depends from claim 1 and limits the method to one wherein detection of altered processing comprises use of a "flow sorter". Hooper further teaches that "disappearance of the membrane-bound form can be followed by, for example, flow cytometry" (pg 275). Therefore, the teachings of Hooper also anticipate claim 46.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al, 1997. Biochem J. 321: 265-279 (cited on the 9/26/07 IDS), as applied to claim 1 above, and further in view of Mucke et al, U.S. Patent 6,175,057 (published January 16, 2001; cited on the 9/20/07 IDS).

The teachings of Hooper are described above. Hooper further teaches that "considerable effort is being expended to find inhibitors of APP β-secretase and γ-secretase with a view to reducing amyloid burden for Alzheimer's disease" (pg 277). Hooper does not teach a method of screening wherein an agent that alters processing is from a compound library.

Mucke teachings methods of screening for agents that affect molecular phenomenon associated with Alzheimer's disease. Mucke teaches that candidate

agents include those from "libraries of synthetic or natural compounds" (col 16, lines 44-45) or "combinatorial libraries" including those made by "chemical means" (col 16, lines 53-54). Mucke further teaches that candidate agents include those with "functional groups necessary for structural interaction with proteins" (col 16, line 33).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute any of the agents suggested by Mucke for the inhibitors used in the method taught by Hooper. The person of ordinary skill in the art would be motivated to do so in order to identify new inhibitors of the secretases involved in Alzheimer's disease. Further, a person of ordinary skill in the art would have a reasonable expectation of success because the method simply requires using the libraries described by Mucke in the screening assays fully described by Hooper.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646